



## **$\alpha$ -Tocopherol and $\beta$ -Carotene Supplements and Lung Cancer Incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: Effects of Base-line Characteristics and Study Compliance**

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**Abstract:** *Background:* Experimental and epidemiologic investigations suggest that  $\alpha$ -tocopherol (the most prevalent chemical form of vitamin E found in vegetable oils, seeds, grains, nuts, and other foods) and  $\beta$ -carotene (a plant pigment and major precursor of vitamin A found in many yellow, orange, and dark-green, leafy vegetables and some fruit) might reduce the risk of cancer, particularly lung cancer. The initial findings of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) indicated, however, that lung cancer incidence was increased among participants who received  $\beta$ -carotene as a supplement. Similar results were recently reported by the Beta-Carotene and Retinol Efficacy Trial (CARET), which tested a combination of  $\beta$ -carotene and vitamin A. *Purpose:* We examined the effects of  $\alpha$ -tocopherol and  $\beta$ -carotene supplementation on the incidence of lung cancer across subgroups of participants in the ATBC Study defined by base-line characteristics (e.g., age, number of cigarettes smoked, dietary or serum vitamin status, and alcohol consumption), by study compliance, and in relation to clinical factors, such as disease stage and histologic type. Our primary purpose was to determine whether the pattern of intervention effects across subgroups could facilitate further interpretation of the main ATBC Study results and shed light on potential mechanisms of action and relevance to other populations. *Methods:* A total of 29 133 men aged 50-69 years who smoked five or more cigarettes daily were randomly assigned to receive  $\alpha$ -tocopherol (50 mg),  $\beta$ -carotene (20 mg),  $\alpha$ -tocopherol and  $\beta$ -carotene, or a placebo daily for 5-8 years (median, 6.1 years). Data regarding smoking and other risk factors for lung cancer and dietary factors were obtained at study entry, along with measurements of serum levels of  $\alpha$ -tocopherol and  $\beta$ -carotene. Incident cases of lung cancer ( $n = 894$ ) were identified through the Finnish Cancer Registry and death certificates. Each lung cancer diagnosis was independently confirmed, and histology or cytology was available for 94% of the cases. Intervention effects were evaluated by use of survival analysis and proportional hazards models. All  $P$  values were derived from two-sided statistical tests. *Results:* No overall effect was observed for lung cancer from  $\alpha$ -tocopherol supplementation (relative risk [RR] = 0.99; 95% confidence interval [CI] = 0.87-1.13;  $P = .86$ , logrank test).  $\beta$ -Carotene supplementation was associated with increased lung cancer risk (RR = 1.16; 95% CI = 1.02-1.33;  $P = .02$ , logrank test). The  $\beta$ -carotene effect appeared stronger, but not substantially different, in participants who smoked at least 20

cigarettes daily (RR = 1.25; 95% CI = 1.07-1.46) compared with those who smoked five to 19 cigarettes daily (RR = 0.97; 95% CI = 0.76-1.23) and in those with a higher alcohol intake ( $\geq 11$  g of ethanol/day [just under one drink per day]; RR = 1.35; 95% CI = 1.01-1.81) compared with those with a lower intake (RR = 1.03; 95% CI = 0.85-1.24). **Conclusions:** Supplementation with  $\alpha$ -tocopherol or  $\beta$ -carotene does not prevent lung cancer in older men who smoke.  $\beta$ -Carotene supplementation at pharmacologic levels may modestly increase lung cancer incidence in cigarette smokers, and this effect may be associated with heavier smoking and higher alcohol intake. **Implications:** While the most direct way to reduce lung cancer risk is not to smoke tobacco, smokers should avoid high-dose  $\beta$ -carotene supplementation.